REMARKS

Claim 1 has been amended to correct a spelling error. Support for the amendment to claim 1 may be found at, *inter alia*, page 12, lines 19-23, 26-27 and 21-32. Claims 1 and 18-25 remain pending in the application. Applicants submit that the amendment to claim 1 raises no issues of new matter and is fully supported by the specification as filed. Applicants respectfully request that this Amendment be entered.

Information Disclosure Statement

The Examiner stated on page 3, paragraph 3 of the April 30, 2010 Office Action that while Applicants have filed an IDS on October 17, 2005, the instant specification cites many patent and non-patent literature references throughout the disclosure that have not been submitted on an IDS. Applicants note that the Information Disclosure Statement filed on April 2, 2010 listed all of the references referred to by the Examiner with the exception of The AOAC Official Methods of Analysis, 1984, nr 43.263 and 43.264. Applicants do not immediately have available The AOAC Official Methods of Analysis, 1984, nr 43.263 and 43.264, but will submit a copy if it can be located. Applicants maintain that the references discussed in the specification of the present application have now all been properly listed in an

Information Disclosure Statement. Accordingly, Applicants respectfully request that this ground of objection be withdrawn.

Claim Objections

Claim 1 was objected to because the spelling of "guanidine acetic acid" is incorrect on line 7. In response, Applicants have amended claim 1 to properly spell "guanidine acetic acid". Applicants respectfully request withdrawal of the Examiner's objection.

Claim Rejection - 35 U.S.C. §103

The Examiner rejected claims 1 and 18-25 under 35 U.S.C. § 103(a) as being unpatentable over McCoy in view of Hageman, WO 99/03365 (hereinafter "Hageman") further in view of Swaisgood, 1993, J. Dairy Sci., 76, pp. 3054-3061 (hereinafter "Swaisgood").

Applicants maintain that claim 1 as amended and claims 18-25 are patentable over McCoy in view of Hageman further in view of Swaisgood. The Examiner alleges that McCoy discloses a nutritional composition of low casein, supplemented with methionine and glycocyamine which reads on the instant claim 1 as the composition of McCoy comprises casein protein and glycocyamine and is free of *free* glycine. The Examiner

acknowledges that McCoy does not disclose that the casein protein used in the composition has a L-serine to glycine ratio more than 2.7:1 as required by the instant claims, but alleges that Swaisgood discloses that casein is a mixture of proteins, some of which proteins have an L-serine:glycine ratio of more than 2.7:1. The Examiner also asserts that Hageman discloses a nutritional composition comprising casein as the protein as well as the components recited in claims 18-25, wherein the composition is free of *free* glycine. The Examiner states that it would have been obvious to one of ordinary skill in the art to combine the teachings of McCoy, Swaisgood and Hageman to arrive at the instant nutritional composition comprising protein containing L-serine andglycine, glycocyamine, carbohydrate, aldehyde, mineral, creatine and vitamins. The Examiner also states that Applicants noted that Swaisgood provides examples of protein sources, i.e. specific casein proteins, wherein the ratio of L-Serine:Glycine is more than 2.7:1 in their February 12, 2010 response regarding a rejection under 35 USC 112.

In response, Applicants note that claim 1 does not mention "free glycine" at all but rather requires that the composition be either i) free of *any* glycine, including any glycine that may be in the amino acid content of proteins and peptides present in

the composition, or, ii) if glycine is present, that the composition satisfies the requirement of a minimum L-Serine:glycine weight ratio of 2.7:1. Contrary to the Examiner's allegations, Applicants note that the compositions of McCoy and Hageman contain casein and thus contain glycine. Accordingly, Applicants note that the mixtures disclosed in McCoy and Hageman *do* contain glycine and therefore do not fall within category (i) above. Applicants further note that "casein", as that term is understood by those of ordinary skill in the art, refers to the protein precipitating from milk near pH 4.6 and refers to a *mixture* of several components which are difficult to separate, such as α_{s1}, α_{s2}, β and κ casein. See Walstra et al., Dairy Science and Technology, 2nd ed. 2006, p. 74-75, 79 (a copy of which is attached hereto as **Exhibit 1**). Applicants further note that Swaisgood itself indicates that the various caseins are difficult to resolve. See Swaisgood, p. 3055, right column. Accordingly, it would not be obvious to one of skill in the art to contemplate *selecting* an individual component from "casein" upon reading McCoy. Applicants therefore maintain that "casein", as that term is used by one of ordinary skill in the art, contains a "mixture" of different components, which, in total, contain L-Serine:Glycine in a ratio of 2.6:1, (as evidenced by Table 23.12 of a handbook authored by

H.G. Kessler, a copy of which is attached hereto as **Exhibit 2**), which is lower than the minimum requirement of 2.7:1 recited in claim 1. Accordingly, the features of the present invention as recited in amended claim 1 are not found in the teachings of McCoy, Hageman, and/or Swaisgood, either alone or in combination. Applicants submit that independent claim 1 defines patentable subject matter over McCoy in view of Hageman in further view of Swaisgood. Claims 18-25 depend from claim 1 and are also submitted to define patentable subject matter at least for the reasons set forth above. Reconsideration and withdrawal of this rejection is respectfully requested.

Nonstatutory Obviousness-Type Double Patenting

The Examiner rejected claims 1, 19 and 21-24 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,544,547 ("the '547 Patent") in view of McCoy and in further view of Swaisgood.

Applicants note that the '547 Patent is a national stage entry under 371(c)(1) of PCT application PCT/NL98/00408, which published as Hageman WO 99/03365. Accordingly, the specification of the '547 Patent and the Hageman publication

cited by the Examiner in relation to the rejection under 103(a) are the same. As discussed above, neither the '547 Patent, McCoy nor Swaisgood teach a composition that either is free of glycine or contains L-Serine:Glycine in a ratio of more than 2.7:1. Accordingly, the features of the present invention as recited in amended claim 1 are not found in the teachings of McCoy, Swaisgood, or the '547 Patent, either alone or in combination. Applicants submit that independent claim 1 defines patentable subject matter over the '547 Patent in view of McCoy in further view of Swaisgood. Claims 18-25 depend from claim 1 and are also submitted to define patentable subject matter at least for the reasons set forth above. Reconsideration and withdrawal of this rejection is respectfully requested.

In summary, Applicants submit that they have addressed and overcome all of the objections and rejections stated in the Office Action, and that the application now is in condition for allowance. Applicants request notice to this effect at the Examiner's earliest convenience.

No fee is believed to be required in connection with the

filing of this Communication. However, the Commissioner is hereby authorized to charge any fees required in connection with the filing of this Communication to Deposit Account No. 03-3125.

Respectfully submitted,

Dated: July 29, 2010

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7/29/10

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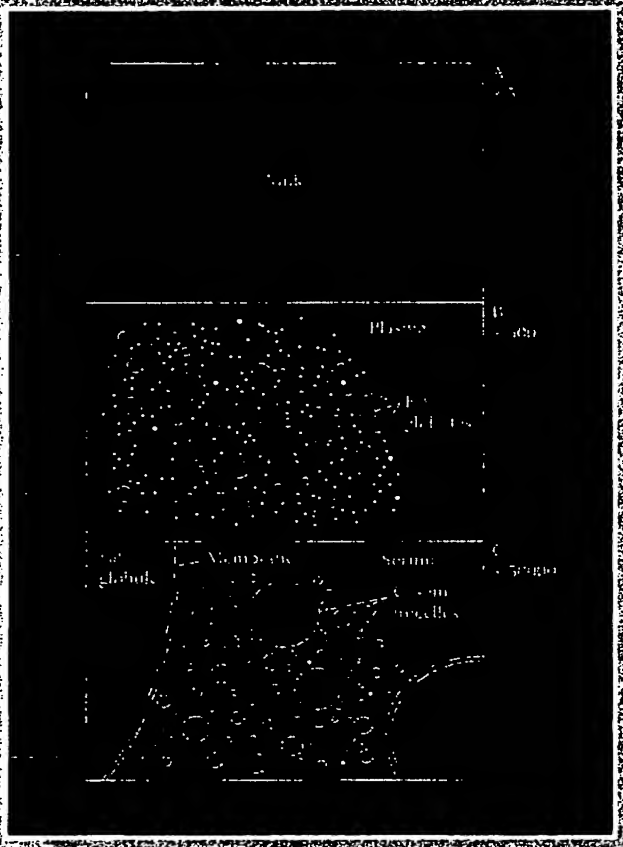

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CRC Taylor & Francis
Taylor & Francis Group
Boca Raton London New York

A CRC title, part of the Taylor & Francis imprint, a member of the Taylor & Francis Group, the academic division of T&F Informa plc.

Published in 2006 by
CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8247-2763-0 (Hardcover)
International Standard Book Number-13: 978-0-8247-2763-5 (Hardcover)
Library of Congress Card Number 2005041830

Library of Congress Cataloging-in-Publication Data

Walstra, Pieter.
Dairy science and technology / Pieter Walstra, Jan T.M. Wouters, T.J. Geurts.--2nd ed.
p. cm. -- (Food science and technology ; 146)
Rev. ed. of: Dairy technology / P. Walstra ... [et al.]. c1999.
Includes bibliographical references.
ISBN 0-8247-2763-0 (alk. paper)
1. Dairy processing. 2. Milk. 3. Dairy products. I. Wouters, Jan T. M. II. Geurts, T. J. (Tom J.)
III. Dairy technology. IV. Title. V. Food science and technology (Taylor & Francis) ; 146.

SF250.5.D385 2005
637'.1--dc22 2005041830

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TABLE 2.14
Some Properties of the Main Groups of Protein in Skim Milk

Property	Caseins	Globular Proteins	Proteose-Peptone
Present in	Casein micelles[a]	Serum	Both
Soluble at pH 4.6	No	Yes	Yes
Clotting by rennet[b]	Yes	No	Partly
Heat denaturation	No	Yes	No

[a] At low temperature part is in the serum.
[b] At pH 6.7.

All the same, the protein composition is well known. Table 2.13 presents an overview of the milk proteins, and Table 2.14 summarizes some practical properties of the main groups. Various chemical properties of the main milk proteins are given in Table 2.15 and amino acid compositions in the Appendix, Table A.5.

Casein is defined as the protein precipitating from milk near pH 4.6. It thus is not soluble at its isoelectric pH. Casein is not a globular protein; it associates extensively and is present in milk in large aggregates, the casein micelles, which also contain the colloidal calcium phosphate (CCP). On acidification, the CCP dissolves.

Casein is a mixture of several components (Table 2.13). According to the genetically determined primary structures, we can distinguish α_{s1}-, α_{s2}-, β-, and κ-casein, but each of these occurs in a number of variants. Most of the κ-casein molecules are glycosylated to various extents. Part of the β-casein is split by proteolytic enzymes into γ-casein and proteose peptone. The α_s- and β-caseins are phosphoproteins that have a number of phosphate groups esterified to serine residues; they precipitate with Ca^{2+} ions, but κ-casein protects them from precipitation. However, κ-casein is easily attacked by the rennet enzyme chymosin, which splits off a portion of the κ-casein molecule; it thereby loses its protective ability. As a result, the casein precipitates in the presence of Ca ions. These reactions are the basis of the clotting of milk by rennet and, thus, of cheese making. Casein altered in this way is called *paracasein* and can be obtained by means of renneting. The resulting rennet casein has a high content of calcium phosphate. (*Note:* Casein and paracasein are chemical names; acid casein and rennet casein are names of commercial products.)

Casein does not show denaturation. However, heating at temperatures above approximately 120°C causes the casein to slowly become insoluble due to chemical changes.

Serum proteins are present in a dissolved form, in the serum. They are often called whey proteins, although they are not precisely identical to the proteins of rennet whey, which also contains the peptides split off from κ-casein. The immunoglobulins in milk vary widely in concentration and composition (colostrum has

TABLE 2.15
Properties of Some Milk Proteins

Property	α_{s1}-Casein (B)	α_{s2}-Casein (A)	β-Casein (A^2)	κ-Casein (A)	β-Lactoglobulin (B)	α-Lactalbumin (B)	Serum Albumin
Molar mass	23,614	25,230	23,983	19,023[a]	18,283	14,176	66,267
Amino acid residues/molecule	199	207	209	169	162	123	582
Phosphoserine (res./mol.)	8	11	5	1	0	0	0
Cysteine (res./mol.)	0	2	0	2	5	8	35
-S-S- linkages/mol.	0	1	0	—	2	4	17
Hexoses (res./mol.)	0	0	0	~2.3[b]	0[c]	0[c]	0
Hydrophobicity[e]	25	23	29	22	29	28	24
α-Helix (approximate %)	7?	?	10?	?	11	30	46
Charged residues (mol %)	34	36	23	21	30	28	34
Net charge/residue	−0.10	−0.07	−0.06	−0.02[b]	−0.04	−0.02	−0.02
Distribution of charge	Uneven	Uneven	Very uneven	Very uneven	Even	Even	
Isoelectric pH	4.5	5.0	4.8	5.6	5.2	~4.3	4.8
Association tendency	Strong	Strong	*f(T)*[f]	Strong	Dimer	No	No
Ca^{2+} binding	++	++	+	-	-	(+)	-

[a] Exclusive of carbohydrate residues.

[b] Average.

[c] 8 in a rare variant (Dr).

[d] A small fraction of the molecules has carbohydrate residues.

[e] % hydrophobic side groups (Val, Leu, Ile, Phe, Trp).

[f] Poor below 5°C, strong (micelle formation) at 37°C.

[g] Binds 1 mol Ca^{2+} per mole; very strong bond.

...serum proteins. Three different degradation products of β-casein (the ...ment of the γ-caseins) largely account for the fraction. It also contains a ...protein (called PP3) that is a fat globule membrane constituent, and pre...ably there are traces of other proteins. Clearly, at neutral pH a considerable ...of the proteose peptone is present in the casein micelles, so that rennet cheese ...by no means contains all of the proteose peptone, but serum obtained upon ...fication of milk does.

Lactoferrin (Table 2.13) is an inhibitor of some bacteria including *Bacillus ...arothermophilus* and *Bacillus subtilis*. The inhibition is caused by removal of ...; more precisely Fe^{3+} ions, from the serum. To be sure, the lactoferrin con...entration in cows' milk is low; in human milk it is far higher.

2.4.4 Casein

The properties of the caseins differ from those of most proteins (Table 2.15; Figure 2.25). Caseins are hydrophobic; they have a fairly high charge, many prolines, and few cysteine residues. They do not form anything more than short lengths of α-helix and have little tertiary structure. This does not imply that the casein molecules are random coils, though in dilute solution the chains are partly unfolded. Many hydrophobic groups are exposed, so that the molecules readily form hydrophobic bonds. The caseins thus show extensive association, both self-association and association with each other. (Association in casein micelles is discussed in Subsection 3.3.1.) The relatively high charge is needed to keep casein in solution.

Casein molecules cannot or can hardly be denatured, because they have little secondary and tertiary structure. An example is given in Figure 2.22. β-lactoglobulin, a globular protein, shows a steep conformational change at about 4-M urea, whereas β-casein changes little. Because of this, casein does not become insoluble by heating at temperatures below 100°C.

The high charge of casein is partly caused by the phosphate groups. These are for the most part esterified to serine residues; near the pH of milk they are largely ionized (Table 2.12). The groups strongly bind divalent ions like Ca^{2+}, especially at a higher pH. Figure 2.26 shows that the Ca binding parallels the content of these groups.

Several different caseins occur in milk, but their separation is not easy. Reactions that cause their precipitation from milk (acidification, renneting, and centrifugation after adding calcium) all yield a more or less complete mixture of caseins. It was only after electrophoresis came into use that resolution of the caseins was feasible, at first into the three components, α, β, and γ. Later on, α-casein could be separated into a fraction sensitive to Ca^{2+} (α_s = α-sensitive) and a Ca^{2+}-insensitive fraction, i.e., κ. Still later, further separation turned out to be necessary to obtain pure components. Currently, the complete primary structures are known. This has revealed that there are four different peptide chains — α_{s1}, α_{s2}, β, and κ, of which the molar ratio is about 11:3:10:4. Differences in phosphorylation and glycosylation, as well as some proteolysis, cause additional heterogeneity.

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ISBN 3-9802378-4-2

Verlag A. Kessler • D-80687 München

Tab. 23.12. Zusammensetzung (%) der Muttermilch und der Milch verschiedener Tierarten [Belitz/Grosch, 1987]

[a] Während der Stillperiode ab dem 15. Tag Anstieg auf 1,6 % Protein.

Art	Protein	Casein	Molkenprotein	Zucker	Fett	Asche
Mensch	0,9[a]	0,4	0,5	7,1	4,5	0,2
Esel	2,0	1,0	1,0	7,4	1,4	0,5
Pferd	2,5	1,3	1,2	6,2	1,9	0,5
Kamel	3,6	2,7	0,9	5,0	4,0	0,8
Rentier	10,1	8,6	1,5	2,8	18,0	1,5
Kuh	3,2	2,6	0,6	4,6	3,9	0,7
Zebu	3,2	2,6	0,6	4,7	4,7	0,7
Yak	5,8			4,6	6,5	0,9
Büffel	3,8	3,2	0,6	4,8	7,4	0,8
Ziege	3,2	2,6	0,6	4,3	4,5	0,8
Schaf	4,6	3,9	0,7	4,8	7,2	0,9
Katze	7,0	3,8	3,2	4,8	4,8	0,6
Hund	7,4	4,8	2,6			
Kaninchen	10,4					

Tab. 23.13. Aminosäurezusammensetzung (g AS/100g Protein) von Gesamtprotein, Casein und Molkenprotein der Kuhmilch [Belitz/Grosch, 1987].

Aminosäure	Gesamtprotein	Casein	Molkenprotein
Alanin	3,7	3,1	5,5
Arginin	3,6	4,1	3,3
Asparaginsäure	8,2	7,0	11,0
Cystin	0,8	0,3	3,0
Glutaminsäure	22,8	23,4	15,5
Glycin	2,2	2,1	3,5
Histidin	2,8	3,0	2,4
Isoleucin	6,2	5,7	7,0
Leucin	10,4	10,5	11,8
Lysin	8,3	8,2	9,6
Methionin	2,9	3,0	2,4
Phenylalanin	5,3	5,1	4,2
Prolin	10,2	12,0	4,4
Serin	5,8	5,5	5,5
Threonin	4,8	4,4	8,5
Tryptophan	1,5	1,5	2,1
Tyrosin	5,4	6,1	4,2
Valin	6,8	7,0	7,5

Tab. 23.14. Wichtige Eigenschaften der vier Caseinkomponenten [Schmidt, 1980; Walstra und Jenness, 1984; Fox, 1989]

Caseinfraktion	α_{s1}	α_{s2}	β	κ
Molekulargewicht (Dalton)	23600	25200	24000	19000
IEP	4,1-4,8	5,1	4,8-5,1	5,5-5,8
Phosphatreste	8-9	10-13	5	1-2
Bindungskräfte für Micellenbildung	H-Brücken hydrophob	elektrostatisch	hydrophob	nicht bekannt
Calciumsensitivität	++	+++	+	-
Nettoladung bei pH 6,6	-21	-16 bis -22	-12	-4

Tab. 23.15. Physikalisch-chemische Charakteristika der Molkenproteinfraktionen [Walstra und Jenness, 1984; Kinsella und Whitehead, 1989]

Fraktion	β-Lg	α-La	BSA	IG
Molekulargewicht (10^3 Dalton)	18,6	14,2	66,0	150-960
Konzentration in Milch [g/kg]	3,2	1,2	0,4	≈ 0,7
pH_{IEP} [-]	5,3	4,8	5,1	5,5-6,8
Cystingruppen [-]	2	4	17	32

Tab. 23.16. Zusammensetzung des Gesamtfettes der Kuhmilch (Gew. %) [Schlimme/Buchheim, 1995]

Bestandteil	
Monoglyceride	0,02 - 0,10
Diglyceride	0,3 - 1,6
Triglyceride	96 - 99
Phospholipide	0,2 - 1,0
Cerebroside	0,01 - 0,07
Squalen	Spuren
Steroide	0,2 - 0,4
Wachse	Spuren
Freie Fettsäuren	0,1 - 0,4

Tab. 23.17. Fettsäurenzusammensetzung von Butterfett [Schlimme/Buchheim, 1995]

		Mittelwert (Gew. %)
4:0	Buttersäure	4,0
6:0	Capronsäure	2,4
8:0	Caprylsäure	1,3
10:0	Caprinsäure	2,9
12:0	Laurinsäure	3,6
14:0	Myristinsäure	11,2
16:0	Palmitinsäure	28,2
18:0	Stearinsäure	9,4
18:1	Octadecensäure	23,5
18:2	Octadecadiensäure	2,1
18:3	Octadecatriensäure	1,7

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Technische Universität München

D-85350 Freising-Weihenstephan

Printed in Germany 1996

ISBN 3-9802378-4-2

kessler - lebensmittel- und bioverfahrenstechnik - molkereitechnologie

D-85350 Freising-Weihenstephan

Verlag A.Kessler, Agnes-Bernauer-Str. 174, D-80687 München